IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Elizabeth M. Denholm, Yong-Qing Lin and Paul J. Silver

Serial No.: 09/715,965 Art Unit: 1654

Filed: November 17, 2000 Examiner: Michael Meller

For: *ATTENUATION OF TUMOR GROWTH, METASTASIS AND ANGIOGENESIS*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-11 and 19-27 in the Office Action mailed May 20, 2003, maintained in the Advisory Action mailed December 11, 2003, in the above-identified patent application. A Notice of Appeal was mailed on October 17, 2003. A Petition for an Extension of Time for three months, up to and including March 17, 2004, is also enclosed. The Commissioner is hereby authorized to charge $165.00 for the filing of this Appeal Brief and $475.00 for a three month Extension of Time, which are the appropriate fees for a small entity. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee BioMarin Enzymes, Inc. Novato, California, and the licensee BioMarin Pharmaceutical Inc., Novato, California.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-11 and 19-27 are pending and on appeal. Claims 12-18 have been cancelled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the amendment mailed on October 17, 2003. In the Advisory Action mailed on December 11, 2003, the Examiner indicated that the amendment would be entered. Appendix I sets forth the claims on appeal.

An amendment is enclosed with this appeal brief to correct antecedent basis. Appendix II sets forth the proposed amended claims. The amendments do not alter the issues on appeal.

(5) SUMMARY OF THE INVENTION

The claims are directed to a method to treat a disorder requiring angiogenesis by administering to a site in an individual in need of treatment an effective amount of a purified chondroitinase to decrease angiogenesis at the site (claim 1). The decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of

capillary-like structures (Page 5, lines 7-10, Example 9 and page 6, lines 5-8; claim 1). The individual can have a disorder in which angiogenesis is involved, such as a disease of excessive or abnormal stimulation of endothelial cells, diseases that have angiogenesis as a pathologic consequence, and scarring following transplantation (page 10, lines 19-28).

The chondroitinase can be a recombinant chondroitinase such as chondroitinase AC from *Flavobacterium heparinum*, chondroitinase B from *Flavobacterium heparinum*, a chrondroitin sulfate degrading enzyme from *Bacteroides* species, a chrondroitin sulfate degrading enzyme from *Proteus vulgaris*, a chrondroitin sulfate degrading enzyme from *Micrococcus*, a chrondroitin sulfate degrading enzyme from *Vibrio* species, a chrondroitin sulfate degrading enzyme from *Arthrobacter aurescens*, and combinations of these enzymes (page 7-8, page 12, lines 24-26). The enzyme can be a mammalian enzyme (page 7, lines 13-16).

The chondroitinase can be administered to an individual having cancer as evidenced by palpable tumors (Example 9). The cancer can be a solid tumor (Example 9). The disorder can be rheumatoid arthritis; psoriasis; ocular angiogenic disease, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; Crohn's disease, atherosclerosis, scleroderma, hypertrophic scarring, adhesions, cirrhosis of the liver, pulmonary fibrosis following acute respiratory distress syndrom or other pulmonary fibrosis of the newborn, endometriosis, polyposis, obesity, uterine fibroids, prostatic hypertrophy, and amyloidosis (page 10, lines 14-23).

The chondroitinase can be administered systematically, locally at or adjacent to a site in need of treatment (page 12, lines 4-16). The chondroitinase can be administered in a controlled

and/or sustained release formulation (page 12, lines 4-16). The chondroitinase can be administered in a dosage range of 0.1 to 250 IU chondroitinase AC/tumor for tumors in the size range from $20mm^3$ to 15 cm^3 (page 12, lines 19-22). The chondroitinase can be administered in combination with another active agent such as antibiotics, cytokines, cytotoxic agents or anti-inflammatories (page 9, lines 26-30). The chondroitinase can be administered after excision of a tumor, using an infusion pump or by topical, intravenous, intracranial or depot routes (page 12, lines 4-16).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-11 and 19-27 are enabled as required by 35 U.S.C. § 112, first paragraph;

(2) whether claims 1-11 and 19-27 are sufficiently described as required by 35 U.S.C. § 112, first paragraph;

(3) whether claims 1, 2, 4-6 and 8 lack novelty under 35 U.S.C. § 102(b) over U.S. Patent No. 4,696,816 to Brown ("Brown");

(4) whether claims 1, 2, 4, 5, 9, 10 and 27 lack novelty under 35 U.S.C. § 102(b) over Takeuchi, *Br J Cancer* 26, 115 (1972) ("Takeuchi");

(5) whether claims 1-5, 8-11, 24, 25 and 27 lack novelty under 35 U.S.C. § 102(b) over WO 96/01648 to Ibex Technologies, Inc ("Ibex");

(6) whether claims 1-11 and 19-27 are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,567,417 to Sasisekharan, et al. in view of Takeuchi, Brown or Ibex.

(7) whether claims 1-11 and 19-27 are obvious under 35 U.S.C. § 103(a) over Takeuchi, Brown or Ibex.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together, as discussed in more detail below. The claims must be examined separately based on the chondroitinase enzyme to be administered (claims 1-5, 20, 24, and 25), the disorders to be treated (claims 6-8 and 26), and the method of administration (claims 9-11, 19, 21-23 and 27).

(8) ARGUMENTS

(a) The Claimed Invention

Angiogenesis is a process whereby new blood vessels form. This is essential in normal development, especially of the fetus, in wound repair, and in weight gain (growth of adipose tissue). It is also essential in some diseases and disorders. The role angiogenesis plays has become of such importance that there is not only a great deal of research in the field to understand the process, but also of inhibitors and growth factors. Copies of the pages from the Angiogenesis Foundation's webpage are enclosed to demonstrate the common knowledge regarding this process and the disorders and disease where it is known that angiogenesis plays a major role.

One major area of interest involves tumors. Tumor metastasis is the process by which malignant cancer cells escape from a tumor and spread throughout the body to develop into multiple secondary tumors. Escape from the primary tumor and invasion into other organs is a complex multi-step process. Metastasis involves changes in tumor cell adhesion and motility,

secretion of proteolytic enyzmes, chemoattractants and proteoglycans. Angiogenesis is also a vital step in the metastatic process. Agents that inhibit angiogenesis have been shown to be effective in inhibiting growth of tumors.

Angiogenesis involves the proliferation and migration of normal endothelial cells, not tumor cells. Appellants have shown that a highly purified and specific glycosaminoglycan degrading enzyme chondroitinase AC and, to a lesser extent chondroitinase B, can be used to inhibit angiogenesis by inhibiting endothelial cell migration and proliferation. This is demonstrated using well accepted *in* vitro and *in* vivo models of angiogenesis. The enzymatic removal of chondroitin sulfates A and C, and to a lesser extent, chondroitin sulfate B, decreases angiogenesis by inhibiting both endothelial cell proliferation and capillary formation.

Decreasing the formation of new blood vessels effectively inhibits angiogenesis, which in turn effectively treats disorders which are dependent on angiogenesis. Representative disorders that are angiogenic dependent are described on pages 10 and 11.

Example 5 demonstrates that chondroitinase AC inhibits endothelial cell proliferation in a dose dependent manner (see Figure 7). Example 6 demonstrates that chondroitinase inhibits angiogenesis, measured as inhibition of capillary-like structures, in a dose-dependent manner (see Figure 5). The remaining examples demonstrate that chondroitinases can be used to inhibit tumor cell proliferation and migration. At the time this application was filed, with priority to November 1999, it was not known that enzymes that cleave chondroitin sulfates could be used to inhibit *angiogenesis*. It was not known that enzymes that could cleave chondroitin sulfates could

inhibit tumor cell proliferation or migration in a dose-dependent manner. It is this discovery that appellants made that forms the basis of the claimed methods.

(b) Rejections of claims 1-11 and 19-27 Under 35 U.S.C. § 112, first paragraph (enablement)

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the

quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

The Claims are Enabled Under this Standard

1. *The claimed chondroitinase enzymes are known, available and well characterized.*

The amino acid sequences and enzymatic activities of the chondroitinases to be used in the claimed methods were known at the time this application was filed. See pages 6-8 of the application.

For example, a review of the specification at page 7, beginning at line 23, makes clear that chondroitinases AC and B from a variety of bacteria and from mammalian sources were known, cloned, isolated and characterized as of the filing date of this application. Enzymes are categorized based on their substrate specificity. In this case, Appellants have defined the critical features of the enzymes that are demonstrated by the examples. The examiner has provided no basis for saying that the chondroitinase isolated from one bacteria or from a mammalian source

is any different from a chondroitinase isolated from a different source. The knowledge regarding an "enzyme" is not defined by or limited by its origin (i.e., *F. heparinum*) but by its enzymatic activity and substrate specificity.

The level of skill in the field of biotechnology is high. One of skill in the art could easily obtain the chondroitinase enzymes and practice the claimed method with routine experimentation (page 7, lines 23-30 of the specification). Protein expression and/or purification methods are well established and routine in the art.

2. *The Methods of Administration and Calculation of Effective Dose are Provided*

Administration protocols and formulations are provided at pages 8, 9 and 12 of the specification, as well as demonstrated by reference to the multiple examples and accompanying figures. The examples show the dose-dependency of the enzyme activity, and what is an effective dosage range. See, for example, Figure 4. Example 9 describes administration of chondroitinase to a mouse tumor model. Figure 8 shows the results of *in vivo* administration of chondroitinase as a function of treatment - it is quite clear that the enzyme was administered in an amount effective to significantly decrease tumor size relative to untreated control. One of skill in the art would need to perform minimal experimentation to obtain and administer the chondroitinase used in the claimed method.

3. *Disorders associated with Angiogenesis are known.*

As described at pages 10-11, appellants have provided numerous examples of angiogenic dependent disorders. Attached is a document as further evidence that those not even skilled in the art are familiar with what is meant by angiogenic dependent disorders.

4. *The Application Contains Numerous Working Examples*

The examples provide further evidence of what disorders can be treated, what enzymes are to be used (example 1 demonstrates how to determine enzyme substrate specificity), what dosages are effective, and what assays can be used to verify efficacy.

Example 5 demonstrates inhibition of endothelial cell proliferation in a dose dependent manner following treatment of chondroitinase AC. Endothelial cells make up new blood vessels and proliferation is required for angiogenesis. Example 6 on page 17 demonstrates that inhibition of growth of capillary-like structures in an in vitro angiogenesis assay after treatment with chondroitinase AC. Growth of new capillaries is required for angiogenesis. Example 8 on page 18 demonstrates that chondroitinase AC treatment can increase apoptosis in vascular endothelial cells, further showing that the claimed method is generally applicable. Induced programmed cell death in vascular endothelial cells can decrease established blood vessels and prevent new ones from forming. Example 9 on page 19 describes treatment of C57BL mice with *established* palpable tumors by administering 55 IU of chondroitinase AC. A solid tumor cannot grow beyond 2-3 mm^3 unless it has an independent blood supply to deliver the oxygen and nutrients it needs to advance and spread. Palpable tumors such as those described in Example 9 are large enough to possess an independent blood supply. Tumor size significantly decreased in the treated mice compared to untreated controls. This example shows an actual reduction to practice of the claimed method.

Summary

The specification clearly describes what enzymes, how to use the enzymes, effective dosages, and what patients are to be treated. The specification gives concrete examples showing the actions of these compounds on endothelial cell proliferation, formation of capillary-like structures and tumor growth. In view of the factors listed in *In re Wands*, one of skill in the art would be fully enabled to practice the claimed method using the teachings of the specification in combination with the knowledge and availability of the compounds in the art. The legal standard has been met.

© **Rejection of claims 1-11 and 19-27 under 35 U.S.C. § 112, first paragraph (written description)**

The Legal Standard

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed. *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000).

A specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and

determined that the invention would work for its intended purpose. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998).

The Claims satisfy the written description requirement

Claim 1 recites

A method to decrease angiogenesis comprising

Administering to a site in an individual in need of treatment thereof for an established disorder requiring angiogenesis an effective amount of a purified chondroitinase to decrease angiogenesis at the site,

Wherein the decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of capillary-like structures.

The language at issue is "an established disorder requiring angiogenesis". Disorders requiring angiogenesis are listed on pages 10-11 of the specification. Metastasis of an established tumor is described on page 1, line 22 to page 2, line 3 as requiring angiogenesis. A tumor larger than 2-3 mm^3 requires angiogenesis to supply nutrients to the tumor. Thus, once a tumor is palpable or large enough to break through the basal lamina and enter the bloodstream, it is established in the host. On page 10, line 8 it states that chondroitinases are used "to inhibit formation, growth and/or metastasis if tumors." In order to inhibit growth and/or metastasis of a tumor, the tumor first needs to be established. If a tumor is not established, it can not grow or metastasize. Similarly on page 6, lines 11-14 the actions of chondroitinase AC and chondroitinase B regulate tumor growth and metastasis by decreasing endothelial cell proliferation and capillary formation and thereby reducing tumor cell access to the bloodstream.

Example 6 on page 17 of the specification describes the inhibition of growth of capillary-like structures in an *in vitro* angiogenesis assay after treatment with chondroitinase AC. Example 9 on page 19 describes the treatment of a mouse with cancer, an established disorder characterized by palpable tumors, with chondroitinase AC. The examples of the specification demonstrate that at the time of filing, the Appellants were in possession of the claimed invention.

There is clear support for the term "an established disorder requiring angiogenesis" in the specification. Appellants are not claiming "the disorder" only the method of treatment.

Claims 6-8 and 26 further define the established disorder requiring angiogenesis. These disorders are explicitly described on pages 9 and 10 of the specification. The written description requirement has been satisfied.

Claims 9-11 and 19 further define the routes of administration of the chondroitinase. These routes of administration are explicitly described on page 12 of the specification. Furthermore, these routes of administration are commonly used in the art. The written description requirement has been met.

(d) Rejections Under 35 U.S.C. § 102

The Legal Standard

For a rejection of claims to be properly founded under 35 USC §102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

It has recently been affirmed that to serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003); *Elan Pharmaceuticals, Inc. v. Mayo Foundation* (October 2, 2003; Fed. Cir. 001467). *See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention."); *PPG Industries, Inc. v. Guardian Industries*

Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.").

The Prior Art

Brown

Brown discloses the use of chondroitinase, as well as collagenase, to break down cartilaginous tissue. See col. 4, lines 25-27 and 42-45. Cartilagious tissue is avascular. There is no disclosure of using chondroitinase or any other glycoasminoglycan degrading enzyme to prevent angiogenesis, in non-cartilaginous tissue or the migration and proliferation of endothelial cells.

Brown does not disclose the claimed method of decreasing angiogenesis in a disorder requiring angiogenesis. The examiner makes two incorrect statements. The first is that Brown teaches treating a tumor with chondroitinase AC (no citation to where is provided). The ***only*** statement with respect to tumors is found at col. 4, lines 42-45, is as follows:

"The enzyme's pharmaceutical use is not limited to a nucleus pulposus, but should find application in the treatment of ganglia, arthroscopy of joints, certain eye conditions, tumors and other unwanted cartilage tissue." (Emphasis added)

This statement is not a teaching, but a speculation. There is nothing enabling about it. There is no teaching of the disorder to be treated, how, when or how much enzyme is to be administered, nor even the criteria for success. Regardless, since it is still with reference to

cartilaginous tissue, it cannot disclose the claimed method which requires inhibiting angiogenesis, i.e., the growth of blood vessels, since ***Cartilage is an avascular tissue.***

The second incorrect statement is that one inherently inhibits angiogenesis merely by administering an enzyme to a site where tumor cells are subsequently injected. As demonstrated by example 6, the effect on angiogenesis is dose dependent. If insufficient enzyme is administered, no efficacy will be observed.

Claims 6-8 define the disorder to be treated by decreasing angiogenesis. As described above, Brown does not disclose an effective amount of chondroitinase to treat these disorders nor does Brown disclose inhibiting angiogenesis. Brown does not meet the legal standard to anticipate the claimed method.

Takeuchi

Takeuchi administers enzyme **prior to or at the time of injecting mice with** tumor cells and shows that the tumor cells do not grow as well. Takeuchi does not demonstrate that one can inject enzyme into established tumors and inhibit further growth, nor inhibit angiogenesis – which requires endothelial cells. All of Takeuchi's studies were done solely on and assessing tumor cells, not on solid tumors of a size requiring vascularization to survive, not over a period of time showing inhibition of metastasis.

The examiner's statement that the mechanism is the same since the method steps are the same is not correct. Takeuchi does not inhibit angiogenesis, nor indeed tumor growth, but some other mechanism which inhibits the injected cells from forming tumors. The data at col. 1 of

page 118 and the discussion at col. 1, of page 119, indicates that the proposed mechanism has nothing to do with angiogenesis.

The Board's attention is drawn to example 7, page 18, and Figures 6 and 7, of the present application. These examples demonstrate that the chondroitinase (1) must not only be provided in an effective dosage to inhibit growth and proliferation of endothelial cells, but (2) that it must be provided in an effective dosage to inhibit growth and proliferation of cells within established tumor cells that are unable to survive absent vascularization, that are not issues for isolated cells. These include tumor cell invasion, endothelial proliferation and angiogenesis.

Those skilled in the art know that merely inhibiting growth of some cells injected at the same time as the treatment is not predictive of success in treating an established disease. Many laboratory mice have been cured under the same conditions Takeuchi uses. There is not much need to cure laboratory mice that were healthy until injected with tumor cells. There is a real need to treat patients who come in with established disease - disease that does not respond to surgery or chemotherapeutic agents, and disease that remains resistant because it is already deeply established within its host. Example 9 shows that the claimed method is different from that shown by Takeuchi since it shows one can treat ***established, palpable*** tumors as claimed and still be effective.

The Board's attention is drawn to the claim language, which specifically refers to "a method to decrease angiogenesis comprising administering to a site in an individual in need of treatment thereof for an established disorder requiring angiogenesis"

Takeuchi does not show treatment of "an established disorder requiring angiogenesis".

Takeuchi does not show or lead one to a treatment to prevent angiogenesis. Absent guidance to treat an angiogenic dependent disease and a recognition that chondroitinase can be used for this purpose IF the correct dose is administered, Takeuchi simply cannot disclose the claimed method.

Ibex

Ibex describes a method to *modulate wound healing* using proteoglycan degrading enzymes, most preferably by enhancing wound healing or "normalizing" wound healing (i.e., promoting healing but not scarring). Ibex does not disclose a method to decrease angiogenesis in an established disorder that requires angiogenesis - Ibex teaches away from a method to decrease angiogenesis.

A wound is not normally considered a disorder. It is not an established disorder. A wound is an acute trauma. Moreover, the mechanism of action described by Ibex is different. As described in the summary on page 9, at line 22 to page 10, line 30, the preferred enzyme is heparinase 3. The enzyme releases growth factors to cause cell proliferation, not inhibit cell proliferation, which is essential to inhibit angiogenesis.

The Examiner has referred to page 5 of Ibex. The reference on page 5 is not to any method of treatment, but describes the ordinary course of events in wound healing, including migration of keratinocytes and epidermal cells in response to chemoattractant and angiogenic signals. This page indicates that angiogenesis is a normal part of wound healing, not that one should inhibit it, but that one should enhance it.

In summary, Ibex does not describe a method of inhibiting angiogenesis.

Ibex actually teaches away from the claimed method because one of skill in the art would not expect administration of chondroitinase to decrease angiogenesis in view of the disclosure of Ibex.

Claim 8 defines a group of disorders requiring angiogenesis. Ibex does not show a decrease in angiogenesis and therefore does not anticipate a method to decrease angiogenensis in any of the disorders listed in Claim 8.

Ibex does not disclose administering chondroitinase to decrease angiogenesis in an established disorder requiring angiogenesis and therefore methods of administering chondroitinase for this purpose are also not anticipated by Ibex.

(e) Rejections Under 35 U.S.C. § 103

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q.

1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). The "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "[T]he showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

The Prior Art

Sasisekharan

Sasisekharan, et al., describes methods of use of heparinase. Sasisekharan does not disclose the use of a chondrointase nor provide any teaching leading one to use a chondroitinase, which has a different substrate specificity and activity than a heparinase. Nor is there any teaching of what would constitute an effective dosage of a chondroitinase.

The claims are directed to a method for decreasing angiogenesis by administering a chondroitinase. Sasisehkaran discloses a method to inhibit angiogenesis by administering an effective amount of heparinase. Heparinases have been shown to decrease cellular proliferation during wound healing and decrease angiogenesis (See Ibex above). Heparinases are structurally and functionally different from chondroitinases. Even within heparinases, activity depends on which heparinase one is referring to - there are at least three found in *F. heparinum* alone, and the activities of the enzymes are highly depending on the source (bacteria versus mammalian).

Sasisehkaran, Ibex and Brown in Combination

Ibex demonstrates that heparinases and chondroitinases not only have different mechanisms of action but act antagonistically (Ibex Figures 3 and 5). A search of the Ibex application fails to uncover the term "angiogenesis". The Ibex application makes no mention of inhibiting blood vessel growth, migration or proliferation. The Ibex application fails to disclose any disorder characterized by and dependent upon angiogenesis. Therefore the Ibex application fails to make up for the deficiencies of either Sasisehkaran or Brown.

Sasisehkaran teaches one in the art about heparinases, not chondroitinases.

Brown states that one can use enzymes to degrade cartilage, an avascular tissue, not that one can inhibit angiogenesis.

In combination, one of skill in the art would be led to use heparinases (Sasisehkaran) to enhance wound healing (Ibex) by increasing proliferation of cells (Ibex), or to degrade cartilage (Brown) or inhibit dissociated tumor cell proliferation (Takeuchi). There is no teaching to combine. There is nothing "clear and particular" that would lead one to have a reasonable

expectation of success by combining and modifying the references as Appellants have done. Therefore the combination does not make obvious the claimed method.

Claims 6-8 and 26 define the disorders to be treated by administering chondroitinase. Sasisehkaran, Ibex and Brown in combination do not make obvious the claimed method regardless of which disorder requiring angiogenesis is to be treated.

The prior art does not teach what an effective amount of enzyme would be to inhibit angiogenesis. As the data in the application demonstrates, dosage is critical - and it is not obvious. The correct dosage must be empirically determined - not for the disease, but for the mechanism by which it is to be treated - in this case, by limiting the blood vessels that feed the disease.

There is no motivation to combine the elements defined by Appellants' claims, much less to treat the disorders as defined by claim 8, or in treating tumors as defined by claims 6, 7, and 21. There is no teaching in any of the references to administer enzyme systemically, or in controlled or sustained release forms. There is no teaching to use chondroitinase B to treat a disorder characterized by angiogenesis. There is no teaching of any combination therapy.

Even if motivation to combine, and the elements missing from the cited art, were suddenly to appear, there is nothing that would lead one to any expectation of success. In the field of cancer, there is no expectation of success based on studies in which dissociated tumor cells are treated *ex vivo*, or at the same time as they are injected into an animal. The literature is replete with failures based on such data. This data is simply not predictive of success in treating

established tumors. Therefore the cited references do not make obvious claims 9-11, 19, 21-23 and 27.

Takeuchi, Brown or WO 96/01648 (Ibex) in Combination

Takeuchi describes inhibition of dissociated tumor cell proliferation. Ibex describes using a glycosaminoglycanase, preferably heparinase, to promote cellular proliferation to enhance wound healing. Brown describes degrading cartilage, an avascular tissue. The cited art does not teach that chondroitinases can inhibit blood vessel growth, migration or proliferation, if administered in the correct dosage.

There is no motivation to combine these references.

There is nothing leading one to modify the references to arrive at the claimed methods.

There is nothing that would lead one to have a reasonable expectation of success using the claimed method to inhibit angiogenesis. Therefore claims 1-5, 20, 24 and 25 are not obvious over Takeuchi in view of Ibex and Brown alone or in combination.

Claims 6-8 and 26 define the disorders to be treated by administering chondroitinase. Takeuchi, Ibex and Brown in combination do not make obvious the claimed method regardless of which disorder requiring angiogenesis is to be treated, none of which are disclosed by the cited art.

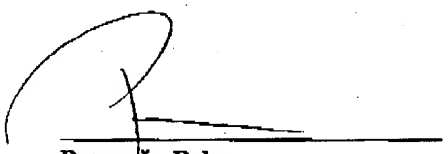
Takeuchi, Ibex and Brown do not teach what an effective amount of enzyme would be to inhibit angiogenesis. Without the appropriate dosage amount, there would be no reasonable expectation of success.

(9) SUMMARY AND CONCLUSION

Appellants have invented a method to treat angiogenic dependent disorders by administering an effective amount of a chondroitinase. This method has great potential therapeutic value in treating disorders including palpable solid tumors, scarring, pulmonary fibrosis and other disorders, many of which have not been successfully treated using available therapies. The claims have been adequately described by the specification. Detailed guidance has been provided in combination with numerous examples of actual reduction to practice. The claimed method is neither anticipated nor rendered obvious by the cited art alone or in combination.

For the foregoing reasons, Appellant submits that the claims 1-11 and 19-27 are patentable.

Respectfully submitted,



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APPEAL BRIEF

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the enclosed Appeal Brief and all documents shown as being attached is being facsimile transmitted to the U. S. Patent and Trademark Office on the date shown below.

Peggy Bailey

Peggy Bailey

Date: February 26, 2004

Appendix: Claims On Appeal

1. (Previously presented) A method to decrease angiogenesis comprising administering to a site in an individual in need of treatment thereof for an established disorder requiring angiogenesis an effective amount of a purified chondroitinase to decrease angiogenesis at the site, wherein the decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of capillary-like structures.

2. (Previously presented) The method of claim 1 wherein the enzyme is selected from the group consisting of chondroitinase AC from *Flavobacterium heparinum*, chondroitinase B from *Flavobacterium heparinum*, a chrondroitin sulfate degrading enzyme from *Bacteroides* species, a chrondroitin sulfate degrading enzyme from *Proteus vulgaris*, a chrondroitin sulfate degrading enzyme from *Micrococcus*, a chrondroitin sulfate degrading enzyme from *Vibrio* species, a chrondroitin sulfate degrading enzyme from *Arthrobacter aurescens*, and combinations thereof wherein these enzymes are expressed from recombinant nucleotide sequences in bacteria.

3. (Original) The method of claim 1 wherein the enzyme is a mammalian enzyme.

4. (Previously presented) The method of claim 8 wherein the enzyme is a chrondroitinase AC.

5. (Previously presented) The method of claim 1 wherein the chondroitinase is chondroitinase AC.

6. (Previously presented) The method of claim 1 wherein the enzyme is administered to an individual having cancer as evidenced by palpable tumors.

7. (Original) The method of claim 6 wherein the cancer is a solid tumor and the enzyme is chondroitinase AC.

8. (Previously presented) The method of claim 1 wherein the individual has a disorder in which angiogenesis is involved, the disorder being selected from the group consisting of rheumatoid arthritis; psoriasis; ocular angiogenic disease, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; Crohn's disease, atherosclerosis, scleroderma, hypertrophic scarring, adhesions, cirrhosis of the liver, pulmonary fibrosis following acute respiratory distress syndrom or other pulmonary fibrosis of the newborn, endometriosis, polyposis, obesity, uterine fibroids, prostatic hypertrophy, and amyloidosis.

9. (Original) The method of claim 1 wherein the enzyme is administered systemically.

10. (Previously presented) The method of claim 1 wherein the enzyme is administered locally at or adjacent a site in need of treatment.

11. (Original) The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.

12. to 18. (canceled)

19. (Original) The method of claim 7 wherein the dosage is in the range of 0.1 to 250 IU chondroitinase AC/tumor for tumors in the size range from 20 mm^3 to 15 cm^3.

20. (Original) The method of claim 1 wherein the enzyme is administered in combination with another active agent selected from the group consisting of antibiotics, cytokines, cytotoxic agents, and anti-inflammatories.

21. (Original) The method of claim 7 wherein the enzyme is administered after excision of the tumor.

22. (Original) The method of claim 9 wherein the enzyme is administered by a route selected from the group consisting of intravenous, intra-cranial, and depo.

23. (Original) The method of claim 9 wherein the enzyme is administered using an infusion pump.

24. (Original) The method of claim 1 wherein the enzyme is chondroitinase B.

25. (Original) The method of claim 8 wherein the enzyme is chondroitinase B.

26. (Original) The method of claim 1 wherein the individual has a disorder in which angiogenesis is involved, the disorder being selected from the group consisting of disease of excessive or abnormal stimulation of endothelial cells, diseases that have angiogenesis as a pathologic consequence, and scarring following transplantation.

27. (Original) The method of claim 1 wherein the enzyme is administered topically.

Appendix II

Proposed Amended Claims

1. (Currently amended) A method to decrease angiogenesis comprising administering to a site in an individual in need of treatment thereof for an established disorder requiring angiogenesis an effective amount of a purified chondroitinase enzyme to decrease angiogenesis at the site, wherein the decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of capillary-like structures.

2. (Previously presented) The method of claim 1 wherein the enzyme is selected from the group consisting of chondroitinase AC from *Flavobacterium heparinum*, chondroitinase B from *Flavobacterium heparinum*, a chrondroitin sulfate degrading enzyme from *Bacteroides* species, a chrondroitin sulfate degrading enzyme from *Proteus vulgaris*, a chrondroitin sulfate degrading enzyme from *Micrococcus*, a chrondroitin sulfate degrading enzyme from *Vibrio* species, a chrondroitin sulfate degrading enzyme from *Arthrobacter aurescens*, and combinations thereof wherein these enzymes are expressed from recombinant nucleotide sequences in bacteria.

3. (Original) The method of claim 1 wherein the enzyme is a mammalian enzyme.

4. (Previously presented) The method of claim 8 wherein the enzyme is a chrondroitinase AC.

5. (Previously presented) The method of claim 1 wherein the chondroitinase is chondroitinase AC.

6. (Previously presented) The method of claim 1 wherein the enzyme is administered to an individual having cancer as evidenced by palpable tumors.

7. (Original) The method of claim 6 wherein the cancer is a solid tumor and the enzyme is chondroitinase AC.

8. (Previously presented) The method of claim 1 wherein the individual has a disorder in which angiogenesis is involved, the disorder being selected from the group consisting of rheumatoid arthritis; psoriasis; ocular angiogenic disease, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; Crohn's disease, atherosclerosis, scleroderma, hypertrophic scarring, adhesions, cirrhosis of the liver, pulmonary fibrosis following acute respiratory distress syndrom or other pulmonary fibrosis of the newborn, endometriosis, polyposis, obesity, uterine fibroids, prostatic hypertrophy, and amyloidosis.

9. (Original) The method of claim 1 wherein the enzyme is administered systemically.

10. (Previously presented) The method of claim 1 wherein the enzyme is administered locally at or adjacent a site in need of treatment.

11. (Original) The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.

12. to 18. (canceled)

19. (Currently amended) The method of claim 7 wherein the chondroitinase is administered in a dosage [[is]] in the range of 0.1 to 250 IU chondroitinase AC/tumor for tumors in the size range from 20 mm^3 to 15 cm^3.

20. (Original) The method of claim 1 wherein the enzyme is administered in combination with another active agent selected from the group consisting of antibiotics, cytokines, cytotoxic agents, and anti-inflammatories.

21. (Original) The method of claim 7 wherein the enzyme is administered after excision of the tumor.

22. (Original) The method of claim 9 wherein the enzyme is administered by a route selected from the group consisting of intravenous, intra-cranial, and depo.

23. (Original) The method of claim 9 wherein the enzyme is administered using an infusion pump.

24. (Original) The method of claim 1 wherein the enzyme is chondroitinase B.

25. (Original) The method of claim 8 wherein the enzyme is chondroitinase B.

26. (Original) The method of claim 1 wherein the individual has a disorder in which angiogenesis is involved, the disorder being selected from the group consisting of disease of excessive or abnormal stimulation of endothelial cells, diseases that have angiogenesis as a pathologic consequence, and scarring following transplantation.

27. (Original) The method of claim 1 wherein the enzyme is administered topically.

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iii. Rejection of Claims 1-5, 8-11, 24, 25 and 27 under 35 U.S.C. § 102(b) over WO 96/01648

(d) Rejections Under 35 U.S.C. § 103

i. Rejection of Claims 1-11 and 19-27 under 35 U.S.C. § 103(a) over Sasisekharan et al. in view of Takeuchi, Brown or WO 96/01648

ii. Rejection of Claims 1-11 and 19-27 under 35 U.S.C. § 103(a) over Takeuchi, Brown or WO 96/01648

(9) SUMMARY AND CONCLUSION

Certificate of Mailing

Appendix I: Claims On Appeal

Appendix II: Proposed Amended Claims on Appeal

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